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Lutein and atherosclerosis: Belfast versus Toulouse revisited

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ABSTRACT

In 1995 we reported that mean plasma lutein concentrations in salaried men and women from Toulouse in Southern France were double those in subjects recruited from general practitioner lists in Belfast, Northern Ireland. At the time incidence of coronary heart disease (CHD) in Southern France was among the lowest in Europe and was much higher in Northern Ireland. Plasma lutein is a biomarker of vegetable and fruit intake and evidence suggests that high concentrations are generally associated with better cardiometabolic health. At the time we speculated like others that role of the carotenoids may well have been to prevent oxidation of lipid in the lipoproteins and so reduce the uptake of oxidised lipid by macrophages and its deposition within the intimal layers of the major arteries as plaque.

It is now widely accepted that CHD is an inflammatory disease and that macrophages within plaque together with tissue damage contribute to this inflammation. Stimulated macrophages release cytokines to activate the immune system both locally and systemically. Precursor complement proteins in the blood are activated to assist immune cells in phagocytosis and cell repair. Individuals with a history of arteriosclerosis display significantly higher concentrations of complement factors C3 and C3a than subjects without such a history. Metabolism of C3 via the alternate complement pathway can give rise to the membrane attack complex (MAC) which creates a hole or pore in pathogens or host cells, killing the cell. Recent studies in patients with early age related macular disease (AMD) who also exhibit similar elevated concentrations of complement proteins in their blood, showed supplementation with lutein progressively decreased the amount of the MAC and other complement factors in the blood. Lutein was used in the supplementation experiments because it is an important constituent of macular pigment. Thus the healthier cardiometabolic features displayed by the people in Toulouse may have been due to the effects of concurrent high concentrations of plasma lutein on the immune system and complement in particular. Other carotenoids may exert similar antioxidant effects but we and others found no differences in antioxidant nutrients between subjects in Toulouse and Belfast or between subjects with asymptomatic markers of atherosclerosis and controls.

Introduction

The Multinational MONItoring of Trends and Determinants in CArdiovascular Disease or the WHO MONICA project began in 1979 and enrolled investigators from 26 countries mainly in Europe. The project was based on the belief that significant differences in disease patterns would be observed between populations that may not be apparent within populations and these would help to reveal underlying mechanisms [1,2]. A uniform dietary surveillance system was set up to examine the dietary habits in the European populations with special regard to cardiovascular diseases. Studies in the city of Toulouse in Southern France revealed a low incidence of coronary heart disease (CHD) and a high intake of fruit and vegetables [3]. In Belfast in Northern Ireland there was a low intake of these foods [4] and the incidence of CHD was 4 fold greater in men and 8 fold greater in women than in Toulouse [2]. In 1992 we studied the blood carotenoid concentrations of people living in these two centres as biomarkers of the fruit and vegetable intake [5].

In collaboration with the two MONICA centres, we obtained blood from middle-aged men and women to investigate the serum carotenoids concentrations and a number of cardiovascular biomarkers [5]. Carotenoids are yellow, orange and red pigments found in the leaves of plants and in fat droplets in a number of fruits [6,7]. Serum carotenoid concentrations are therefore biomarkers of vegetables and fruit consumption and although a

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number of factors may influence absorption, serum carotenoid concentrations are a rough indicator of the amount [8], and sometimes the specific type, of fruit and/or vegetable consumed [9].

There were significant differences in the cardiovascular biomarkers that conformed with the expected CHD risks observed in the two communities but what was very striking was the concentrations of the two hydroxy-carotenoids lutein and β-cryptoxanthin, which were twice as high in Toulouse as in Belfast [5]. At that time we accepted the then current theory of atherogenesis that the anti-oxidant properties hydroxy-carotenoids and other nutrients played a role in preventing CHD by reducing or preventing lipoprotein oxidation [10,11]. However, vitamin E in lipoproteins is a more powerful anti-oxidant than the carotenoids and evidence suggests that vitamin E supplements do not reduce the risk of heart disease [12,13] and other studies found none or inconsistent epidemiological evidence for inverse associations of β-carotene or lycopene with biomarkers of cardiovascular disease [10,11,14].

However, since 1995, evidence has been accumulating that hydroxy-carotenoids may have a role in preventing atherogenesis. In 1997, it was reported that serum lutein and zeaxanthin concentrations were significantly lower in participants with intimal-medial wall thickness (IMT; asymptomatic atherosclerosis) above the population 90th centile than controls [14] and, in 2004, Dwyer and colleagues reported that the 18 month change in IMT was inversely related to lutein, zeaxanthin, β-cryptoxanthin and α-carotene in asymptomatic middle-aged adults [15]. Others noted that lutein predominates in red blood cells and peripheral blood monocytes and its concentration is higher than β-carotene in these tissues [16]. Furthermore much more information has become available on lutein because of its important role as a constituent of macular pigment [17] and also as the probable precursor of meso-zeaxanthin (MZ) [18]. Equal proportions of lutein, zeaxanthin and MZ are the main constituents of macular pigment. All this information up to 2014, was recently reported as a systematic review which concluded that higher blood lutein concentrations were significantly associated with better cardiometabolic health [19].

Lutein is a nutrient and concentrations in the blood are derived from a vegetable diet [7]. Those studies where vegetable intakes have benefited cardiovascular outcomes began in early life or reflect a high consumption of fruit and vegetables from an early age [20–22] before atherosclerotic plaque formation [23]. That is, the effects of dietary nutrients like lutein on health are preventative and not curative. So an ancillary study to the Age Related Eye Disease Study 2 (AREDS-2) which investigated the effects of lutein supplements on cardiovascular outcomes in people with a mean age of 74 years [24] will be discussed later as it was not included in the Leemakers review [19].

The objective of this mini-review is to revisit data obtained in Toulouse and Belfast in 1992–3 and present recent evidence on the effects of lutein on the complement system which suggests a new explanation why diets high in vegetables are beneficial in reducing the risk of CHD. It should be noted that unless specified otherwise, we will use the term lutein to include zeaxanthin. Zeaxanthin is present in most lutein supplements but the amounts are usually less than 10% and zeaxanthin is only 5–10% of dietary intake and plasma lutein concentrations.

Methods used for the Belfast and Toulouse study [5]

In late September 1992, 89 men and 82 women aged 45–65 years were randomly sampled from General Practitioner Lists by the Central Services Agency in Belfast. In April 1993 102 salaried men and 109 women aged 45–64 years were recruited from an alphabetical list in the Social Security files in Toulouse. There were no significant differences between the mean ages of the men (55 years) or the women (53 years) in the two samples. Ethical approval was obtained from appropriate committees in both centres. Personal details from each subject included body mass index (BMI), blood pressure, smoking habits and dietary questionnaires.

Fasting blood plasma and serum were separated immediately and stored at −70 °C. Plasma lipids and lipoproteins were determined using conventional kits (Instrument Laboratories Ltd, Cheshire). Retinol, α- and γ-tocopherol and a carotenoid profile were determined by high pressure liquid chromatography on plasma stored approximately 8 (Belfast) and 2 (Toulouse) months respectively [25]. The carotenoids are known to be stable over this period [26]. The analyses were done at the University of Ulster laboratories in Coleraine. The site of origin of the samples was known to laboratory staff so samples from both centres were analysed in all batches to minimise bias. Lutein was not separated from zeaxanthin by this method.

Comparisons of the blood cardiovascular risk factors and carotenoid concentrations in Toulouse and Belfast

Data collected on cardiovascular risk factors included weight and height to calculate BMI, total, high (HDL) and low-density lipoprotein cholesterol (LDL), triglycerides and lipoproteins A1, B and (a). Since the incidence of CHD in Belfast was significantly higher than that in Toulouse [1,2], concentrations of all risk factors except lipoprotein-(a) reflected this in the women. In the men, the data were similar to those in the women but there were no differences in BMI, total or LDL cholesterol and lipoprotein-(a) between the two centres (data shown in [5]). Hypertension (defined by diastolic ⩾95 mmHg and/or systolic >160 mmHg, or on antihypertensive therapy) was more prevalent in Belfast (24%) than Toulouse (11%).There were twice as many current smokers in Belfast than in Toulouse in this study [5] although in a separate report on smoking in all MONICA centres in 1988, there were very similar numbers of current smokers in Belfast (46%) and Toulouse (43%) [27].

The data obtained on plasma micronutrient concentrations are shown in Table 1. The important observation was that concentrations of the xanthophyll carotenoids, lutein and β-cryptoxanthin, were twice as high in Toulouse as in Belfast in both men and women. Furthermore concentrations of β-carotene and lycopene, the other two main carotenoids in plasma, and the α-tocopherol: cholesterol ratios were not different in either men or women between the two centres.

Plasma carotenoid concentrations reflect the dietary intake of vegetables and fruit [6,7] but many factors can influence bioavailability [28,29] and usually lutein in green vegetables is poorly bioavailable. Bioavailability is promoted by cooking, macerating, mincing or chewing [28] and by inclusion of fat [29] in the food preparation. The mean concentration of plasma lutein in the Belfast subjects was very similar to median concentrations of lutein (0.25 μmol/L) in both sexes in a nationally representative sample in England and Wales [30]. Time of year will affect the diversity of vegetable and fruit intakes and the two studies were done in different seasons namely Autumn (September, Belfast) and Spring (April, Toulouse) the following year. However the different times of collection are unlikely to explain the large differences in lutein concentration between the two centres. A study in Cambridge UK in which vegetables and fruit intakes and blood carotenoids in 42 women aged 50–65 years were measured in the 4 seasons, did not find such big differences in lutein concentrations between the seasons as found between Belfast and Toulouse [8]. The Cambridge study examined 4-day weighed vegetable and fruit intakes and blood concentrations of lutein, lycopene and β-carotene in the